REMARKS

Restriction Requirement

Applicants note that the Examiner has made the Restriction Requirement final, and has noted that Claims 4-7 and 10 have been withdrawn from consideration, *there being no allowable generic or linking claim*. Applicants have not cancelled Claims 4-7 or 10 in the event that a linking or generic claim is found to be allowable. Moreover, claims of Groups II and III remain in the application and will be amended throughout prosecution to be commensurate in scope with the product claims, pursuant to the request for rejoinder. Claims from Group IV have been cancelled, without prejudice to or disclaimer of the subject matter therein. Applicants expressly reserve the right to pursue the subject matter of any non-elected claims in a divisional application, without the need to file a terminal disclaimer.

Priority

The Examiner has objected to the priority claim in that it does not appear in the first sentence of the specification. The specification has been amended to correct this deficiency by moving the priority claim to the proper position after the title.

Objection to the Specification and Rejection of Claims 1, 2, 3, 8, 9, and 11-15 Under 35 U.S.C. § 112, First Paragraph:

The Examiner has objected to the specification and rejected Claims 1, 2, 3, 8, 9, and 11-15 under 35 U.S.C. § 112, first paragraph, on the basis of enablement. Applicants respectfully traverse this rejection.

First, the Examiner states that the specification is enabling for dendritic cells loaded with either whole cell or yeast spheroplasts and an antigen, but asserts that the specification does not enable dendritic cells that are loaded with any yeast vehicle and an antigen. The Examiner points to page 8, lines 14-20 of the specification and submits that it is Applicants' assertion that the yeast cell wall components are likely to be necessary for the operability of the composition, and submits that all yeast vehicles other than the whole cells lack the cell wall, thus allegedly drawing into question whether any yeast vehicle would activate dendritic cells. The Examiner notes that U.S.

Patent 5,830,463 to Duke et al. teach that spheroplasts activate cells and therefore concludes that some other features of yeast allow the vehicles to function, but also concludes that due to inconsistencies between the teachings, all yeast vehicles are not enabled.

In response to this portion of the rejection, Applicants initially note that the Examiner focuses on a discussion of the cell wall components and the contribution of these components to the adjuvant activity of yeast with regard to dendritic cells. However, the Examiner is respectfully referred to the subsequent paragraph which describes other means by which the yeast may enhance the DC-mediated immunization process. More specifically, the Examiner concludes that the specification represents that cell wall components are likely to be necessary for the operability of the claimed composition, while Applicants do not find a portion of the specification that makes such a representation. Rather, as discussed on page 8 through page 9 of the specification, for example, while it has been shown that yeast cell wall components can act as biological response modifiers, the present inventor's data have gone well beyond this simple finding to demonstrate that yeast not only act as a potent adjuvant, but also stimulate the DCs to stimulate both MHC Class I and Class II primary T cell responses. Importantly, as stated on page 9, lines 3-10, the present inventors' data indicate that the "*the efficiency with which recombinant yeast-expressed antigens are processed and presented by DCs cannot be completely accounted for by the adjuvant properties of yeast.* Recombinant yeast appear to provide antigen to DCs in discrete, concentrated packages that are avidly internalized, thereby effectively increasing the amount of antigen available for processing." (emphasis added) Therefore, the present specification concludes it is not simply adjuvant effects (e.g., cell wall components) that contribute to efficacy of the vaccine of the present invention. In fact, the present specification only suggests that yeast cell wall components can contribute to yeast adjuvant effect, but nowhere does the specification conclude that these components are *required* for the efficacy of the claimed vaccine. Indeed, each of the intact yeast, yeast spheroplast, yeast cytoplast, yeast ghost and subcellular yeast particle will have the characteristic of being able to deliver antigens to the DCs in concentrated packages that can be avidly internalized, and this function is independent of cell wall components.

Furthermore, with regard to the reference to the '463 patent, the Examiner contends that a showing in that patent that yeast spheroplasts activate cells and a suggestion that some component of the yeast other than the cell wall allow the yeast to function are inconsistent with the present specification teachings. Based on the discussion above, Applicants submit that this is incorrect, because the present specification clearly teaches that the yeast vehicles have effects that are not accounted for solely by an adjuvant effect. The use of a yeast spheroplast in the '463 patent, in conjunction with the teachings in the present specification, clearly supports Applicants contention that yeast vehicles lacking cell wall components are expected to be operable in the claimed vaccines.

Second, the Examiner contends that the claims read on compositions that are therapeutically effective against any number of different diseases, and asserts that the specification only demonstrates efficacy against two antigen sources, cancer and HIV infection. The Examiner asserts that the specification demonstrates that the compositions would be effective in the induction of some form of immune response, but asserts that the specification does not show that the compositions would be effective against any disease.

In response to this concern, Applicants initially submit that, in contrast to the Examiner's representation, the present specification does in fact demonstrate the compositions of the present invention can provide a therapeutic effect against diseases associated with the antigen source. For example, Example 7 shows that administration of a composition of the present invention in an art-accepted tumor model induced *protective* immunity against tumors expressing the antigen *in vivo*. Moreover, there are multiple examples demonstrating the efficacy of the yeast vehicles expressing an antigen *in vivo* and given that the specification also demonstrates the surprising efficacy of the claimed dendritic cell compositions to elicit immune responses as compared to the yeast vehicle/antigen combination alone, it is reasonably expected that DC compositions comprising the yeast vehicle and antigen would be even more efficacious.

In addition, the present specification provides substantial evidence that the present compositions are capable of eliciting both a cellular (MHC Class I-restricted and MHC Class II-restricted) and humoral immune response against different types of antigens. The specification teaches that an antigen is a moiety which elicits a humoral and/or cellular immune response, such that administration of the antigen elicits an antigen-specific immune response against the same or

similar moiety that is encountered *in vivo*. Applicants submit that, given the data provided in the specification with different antigens, one of skill in the art would expect that the claimed composition would function to elicit an antigen-specific immune response against *any* antigen. The present invention boosts the immune response against a moiety that is already *antigenic*. The Examiner has not provided any basis as to why any antigen would not be operable in the invention. Furthermore, the specification does not require that the claimed composition actually cure or significantly reduce any or all symptoms of a disease, but rather that the composition provide some therapeutic benefit, which can simply include the elicitation of an immune response against a therapeutically relevant antigen (see page 22, lines 15-35). Indeed, many antigens are already known to be therapeutically beneficial in other types of vaccines (e.g., in connection with a conventional adjuvant); therefore, the use of such antigens would be expected to provide a therapeutic benefit in the present composition. It is well known in the art that the primary function of a vaccine is to elicit an immune response, and the elicitation of such immune response would be considered to have a therapeutic benefit in many situations.

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1, 2, 3, 8, 9 and 11-15 under 35 U.S.C. § 112, first paragraph.

Rejection of Claims 1, 6, 11, 13, 14 and 15 Under 35 U.S.C. § 102(b):

The Examiner has rejected Claims 1, 6, 11, 13, 14 and 15 under 35 U.S.C. § 102(b), contending that these claims are anticipated by Sousa et al., which allegedly teach the phagocytosis of *Saccharomyces cerevisiae* by isolated dendritic cells. The Examiner contends that because a yeast cell inherently comprises antigens, the reference anticipates the claimed invention.

Applicants traverse the rejection under 35 U.S.C. § 102(b). Initially, it is noted that in order to clarify what was intended by the claimed invention, the claims have been amended to recite that the antigen is a heterologous antigen with respect to the yeast. Support for this amendment is found, for example, on page 14, lines 4-6 of the specification. Sousa et al. do not teach or suggest such a heterologous antigen and therefore, Sousa et al. do not teach or suggest the presently claimed invention.

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1, 6, 11, 13, 14 and 15 under 35 U.S.C. § 102(b).

Rejection of Claims 1-3, 8, 9 and 11-15 Under 35 U.S.C. § 103:

The Examiner has rejected Claims 1-3, 8, 9 and 11-15 under 35 U.S.C. § 103, contending that these claims are unpatentable over Duke et al. (U.S. Patent No. 5,830,463) in view of Cohen et al. The Examiner asserts that Duke et al. teach a yeast vehicle comprising yeast vehicles that can transport antigens to cell, including dendritic cells. Duke et al. is further alleged to teach delivering yeast particles to the cells *in vitro*, such that the particles can be absorbed by the cells, and then returning the cells to the animal from which they were isolated. The Examiner admits that Duke et al. do not teach the administration of therapeutic compositions comprising each of dendritic cells, a yeast vehicle and an antigen. Cohen et al. is cited for teaching the administration of a recombinant antigen presenting cell to induce an immune response. The Examiner contends that it would be apparent to those in the art that dendritic cells treated by using yeast vehicles to transform the cells would be capable of inducing the same or similar response as those created by the techniques of Cohen et al., and that because Duke et al. and Cohen et al. are concerned with the same problem and create cells having a similar function, one would have a reasonable expectation of success at combining the methods.

Applicants traverse the rejection of Claims 1-3, 8, 9 and 11-15 under 35 U.S.C. § 103. First, Applicants submit that the combination of references fails to teach each and every element of the claimed invention. The claims require a composition comprising a dendritic cell that has been loaded intracellularly with a yeast vehicle and a heterologous antigen. Neither of Duke et al. or Cohen et al. explicitly teach such a composition. To separate the components is to ignore an important element of the invention and particularly, that the dendritic cell should be loaded intracellularly with the combination of the yeast vehicle and the antigen.

Second, Applicants submit that there is no motivation provided by the references or even in the art to combine the references as the Examiner has done. Duke et al. teach the use of a yeast vehicle that carries a heterologous antigen and its use to elicit an immune response in a mammal. At most, Duke et al. motivate one of skill in the art to use that invention, which is the yeast vehicle

carrying a heterologous antigen, as a therapeutic vaccine. There is no teaching in Duke et al. that would lead one of skill in the art to look to another reference to change the way in which the immune response is induced because Duke et al. teach that the yeast vehicle expressing an antigen elicits both a cellular and humoral immune response effectively. Similarly, Cohen et al. teaches the administration of antigen presenting cells (APCs) that recombinantly express an antigen and that have at least one MHC component that is allogeneic to the recipient. This is the solution that Cohen et al. provide to the problem of eliciting stronger and more long lasting T cell immune responses and Cohen et al. teach that this is an effective solution. Moreover, the solution of Cohen et al. relies significantly on the use of APCs that are "semi-allogeneic", which is a distinct solution from that provided by Duke et al. and which does not in any way suggest that one should use a different approach to elicit an immune response. Both Duke et al. and Cohen et al. are issued patents that teach distinct inventions that are solutions to a problem, but neither patent suggests that their invention should be improved, particularly by turning to an entirely different technology. To suggest that one of skill in the art would be motivated to combine the references because they are concerned with the same problem and achieve a similar result (e.g., stimulation of an antigen-specific immune response) is not a reasonable argument because neither of Duke et al. or Cohen et al. lead one to believe that there are any deficiencies in their compositions or methods that would benefit from combining the technologies (i.e., the compositions and methods of Duke et al. and Cohen et al. are distinct means of eliciting an immune response and are taught to be efficacious, and so there is no motivation to make changes to either of the compositions or methods). Indeed, to go beyond the teachings of either cited patent and conclude that one would be motivated to combine the references can only result from a hindsight reconstruction using the claimed invention, which is not an appropriate standard for obviousness.

Morever, there is no teaching or suggestion in either of Duke et al. or Cohen et al. that to combine the technologies would lead to any improvement over what is taught by either of Duke et al. or Cohen et al. alone. In contrast, the present invention represents a surprising and unexpected finding. Specifically, the present inventors have made the unexpected discovery that protective cell-mediated immune responses can be mediated with surprisingly potent results through direct interactions between recombinant yeast and dendritic cells (DCs). Prior to the present invention,

there was no indication that dendritic cells that are prepared by loading yeast-antigen complexes would be extraordinarily efficacious as a vaccine, as compared to other vaccine strategies, including administration of antigen alone or administration of a yeast-antigen complex directly to a mammal (e.g., see Examples 4, 5 and 7).

Therefore, the combination of Duke et al. and Cohen et al. fail to teach or suggest the present invention as claimed. In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1-3, 8, 9 and 11-15 under 35 U.S.C. § 103.

Rejection of Claims 1, 2, 9, and 13-15 Under 35 U.S.C. § 103:

The Examiner has rejected Claims 1, 2, 9 and 13-15 under 35 U.S.C. § 103, contending that these claims are unpatentable over Layton et al. and Adams et al. in view of the teachings of Tomai et al. The Examiner states that a "yeast vehicle" is interpreted to include any particle that is derived from a yeast cell or that comprises yeast components. Layton et al. and Adams are cited as teaching the use of yeast-derived virus-like particles (Ty particles) to deliver antigens to APCs for the purpose of inducing a CTL response against the antigen. Tomai is cited for teaching that mature dendritic cells can induce Th1 (CTL) responses and the loading of dendritic cells with antigens. The Examiner contends that because Tomai et al. teach loading of dendritic cells with antigens and because Layton et al. and Adams et al. teach delivering antigenic peptides to immune cells, it would be obvious to combine these teachings to arrive at the claimed invention. The Examiner asserts that it would be obvious that the Ty particles could be processed and presented by the dendritic cells.

Applicants traverse the rejection of Claims 1, 2, 9 and 13-15 under 35 U.S.C. § 103. First, Applicants submit that the combination of references fails to teach each and every element of the claimed invention. As in the first rejection under § 103 above, neither of Layton et al., Adams et al. or Tomai et al. teach or suggest a dendritic cell that has been loaded intracellularly with a yeast vehicle and a heterologous antigen. To combine the references based on the teaching of individual components ignores the final phrase of Claim 1.

Second, Applicants submit that there is no motivation provided by the references or in the art to combine the references as the Examiner has done. Layton et al. and Adams et al. teach that Ty particles, which are formed from the structural portion of an intracellular transposon protein that

self-assembles into particles in the cytoplasm of a yeast cell, can be made into a fusion protein and elicit an immune response, but neither reference provides any motivation to modify this technique by loading the fusion protein into a dendritic cell. If one turns to Tomai et al. for the motivation to make the combination, one finds that Tomai et al. fail to provide any motivation to load a yeast vehicle and an antigen into a dendritic cell, because Tomai et al. is directed to a completely different means of stimulating dendritic cells to elicit an immune response. Tomai et al. teach the use of imidazoquinoline immune response modifying compounds to induce the maturation of dendritic cells *in vitro*, which can then be used directly and/or exposed to an antigen. The use of imidazoquinoline compounds is the solution that Tomai et al. provide to eliciting an immune response. There is no motivation to look to other techniques such as the provision of a yeast vehicle of the present invention or even a Ty particle fused with an antigen to elicit an immune response.

Finally, the combination of Layton et al. or Adams et al. with Tomai et al. fail to appreciate the surprising and unexpected discovery by the present inventors that protective cell-mediated immune responses can be mediated with surprisingly potent results through direct interactions between recombinant yeast and dendritic cells (DCs). Prior to the present invention, there was no indication that dendritic cells that are prepared by loading yeast-antigen complexes would be extraordinarily efficacious as a vaccine, as compared to other vaccine strategies, as discussed above.

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1, 2, 9 and 13-15 under 35 U.S.C. § 103.

Rejection of Claims 1-3, 8, 9 and 11-15 Under 35 U.S.C. § 103:

The Examiner has rejected Claims 1-3, 8, 9 and 11-15 under 35 U.S.C. § 103, contending that these claims are unpatentable over Duke et al. in view of Tomai et al. The Examiner contends that it would have been obvious to use the antigenic particles of Duke et al. to activate the dendritic cells of Tomai et al., because it would be obvious to combine compositions that perform the same function and to load the dendritic cells of Tomai et al. with the particles of Duke and with free antigen.

Applicants traverse the rejection of Claims 1-3, 8, 9 and 11-15 under 35 U.S.C. § 103. Again, Applicants submit that the combination of Duke et al. and Tomai et al. fail to teach each and

every element of the claimed invention, since a composition comprising a dendritic cell that has been loaded intracellularly with a yeast vehicle and a heterologous antigen has not been provided by either reference, alone or in combination.

Second, the Examiner again seems to contend that the teachings of Duke et al. and Tomai et al. are somehow equivalent and would cause one of skill in the art to simply combine the teachings. However, to neither of Duke et al. or Tomai et al. lead one to believe that there are any deficiencies in their compositions or methods that would benefit from combining the technologies, since Duke et al. teach that there is no need for any other adjuvants such as imidazoquinoline compounds of Tomai et al., and since the solution for Tomai et al. is to provide the imidazoquinoline compounds to boost dendritic cell maturation. The compositions and methods of Duke et al. and Tomai et al. are distinct means of eliciting an immune response and are taught to be efficacious, and so there is no motivation to make changes to either of the compositions or methods, and certainly not to combine the teachings of the references. Again, to go beyond the teachings of either cited patent and conclude that one would be motivated to combine the references can only result from a hindsight reconstruction using the claimed invention, which is not an appropriate standard for obviousness.

Finally, the combination of Duke et al. and Tomai et al. fail to appreciate the surprising and unexpected discovery by the present inventors that protective cell-mediated immune responses can be mediated with surprisingly potent results through direct interactions between recombinant yeast and dendritic cells (DCs). As discussed previously, the results provided by the present specification demonstrate that the loading of DCs with yeast vehicles and antigens is significantly more efficacious than DC exposed to antigen (e.g., Tomai et al.) or yeast vehicles plus antigen (e.g., Duke et al.).

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1-3, 8, 9 and 11-15 under 35 U.S.C. § 103.

Applicants have attempted to respond to all of the rejections in the December 2 Office Action and submit that the claims are in a condition for allowance. In the event that the Examiner has any

remaining questions or concerns regarding Applicants' position, please contact the below-named agent to expedite prosecution.

Respectfully submitted,

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